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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
FOLEY, SHANON A	
ART UNIT	PAPER NUMBER
1648	9

DATE MAILED: 06/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/857,402	AGUILAR RUBIDO ET AL.	
	Examiner	Art Unit	
	Shanon Foley	1648	

-- The MAILING DATE of this communication appears on the cover sh t with th correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication. even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 May 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 September 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant has amended claims 11, 19, 23 and added new claims 24-33 in paper no. 8. Claims 11-33 are under consideration.

Drawings

Figure 5 remains objected to because the language within the drawing is in Spanish. Correction is required accompanied by an assurance that no new matter is introduced. This objection will be maintained until appropriate correction is made.

Response to Amendment

The amendment filed 5/12/02 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The amendment adds a "Summary of the invention" section in which an unsupported concept, "a virus-like particle (VLP) comprising a surface antigen" is added. There is no support for a VLP comprising a surface antigen in the original disclosure.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In response to the rejections under 35 U.S.C. 112, second paragraph, applicant states that the instant composition comprises a VLP and a vaccine antigen, which provides an adjuvant enhancing effect on either the VLP, the vaccine antigen or each other. Applicant has also amended the claims to incorporate mixing the antigens to further define the invention.

Applicant's arguments and the amendments to the claims have been considered. However, claim 11 and all dependent claims remain vague and indefinite because it cannot be determined whether the "mixture" is referring to a physical linkage or fusion or whether the antigens are within the same proximity. Amended claim 11 recites, "a virus-like particle (VLP) *comprising* a surface antigen" (emphasis added). Similarly, claims 31-33 recite that the vaccine antigen *comprises* core or nucleocapsid antigens from HBV, HCV, and HPV, respectively (emphasis added). These limitations encompass direct joining, fusion or linkage and do not exclude a lack of direct physical association. This limitation further confuses the association of the vaccine antigen with the VLP in claim 11 since the VLP comprises not only the surface antigen, but also the non-living vaccine antigen, since the nature of the "mixture" is unclear. Therefore, the amendment to claim 11 does not aid in more clearly defining whether the virus-like particle of claims 16-19 comprising the nucleocapsid antigen is physically joined or not.

Claim 19 is unclear because the claim states that the formulation comprising HBsAg and the vaccine antigen "comprises a single antigen". Is this single antigen in addition to the surface and vaccine antigens, or are the HBsAg and the vaccine antigens one and the same antigen? The claim is also vague and indefinite for the "mixture of different antigens". The nature of the mixture is unclear.

New claims 28-30 are unclear because it cannot be determined in what way the immune response is enhanced or what type of immune response is enhanced.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection maintained for reasons of record.

Applicant argues that the VLPs and the vaccine antigens are mixed together, as described in the original disclosure and the amended claims in such a way as to convey to the skilled artisan that the inventor had possession of the claimed invention at the time of filing.

Applicant's arguments as well as the amendments to the claims have been considered, but are found to be unpersuasive because the nature of the mixture and the "mixing" process is unclear. Mixing encompasses a melding of two different entities into the same proximity or fused to one another. There is no support in the disclosure teaching how the skilled artisan could fuse any viral nucleocapsid to HBsAg or any VLP to any viral surface antigen. The specification does not teach how the skilled artisan could identify a mixture, fusion, or complex of HBsAg and any viral nucleocapsid that would satisfy the intended vaccine function or convey possession of these complexes at the time of filing.

Claims 11-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 11 has been amended to recite, "a virus-like particle (VLP) comprising a surface antigen from a virus". Claim 15 states that the surface antigen is Hepatitis B virus surface antigen (HBsAg) and claims 16-18 state that the a virus-like particle (VLP) comprise nucleocapsid antigens from hepatitis B (HBV), hepatitis C (HCV), or papillomavirus (HPV) nucleocapsid antigens, respectively. Nucleocapsid antigens and surface antigens of hepatitis B are distinctly different, see Figure 1 of Fields et al. on page 2705. There is no support in the original claims or disclosure that would indicate that the VLP comprises, i.e. fused or linked, to a hepatitis B surface antigen, only a hepatitis B nucleocapsid protein.

Claims 22-27 have been amended to recite that the instant vaccine formulation is a therapeutic or a preventative vaccine against HBV, HPV, and HCV, respectively. Although the original claims and the disclosure on page 5, lines 29-31 provide support for vaccine compositions, there is no support for the intended use of the vaccine or the instant formulations being limited to treat or prevent certain types of virus infections. This is a new matter and a written description rejection.

Claims 15-19, 22-27 and 31-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record.

In response to the rejection, applicant states that the amended claims are clear for which disease is being treated.

Applicant's amendments to the claims have been considered, but are found to contain new matter. There is no support for the intended therapeutic or preventative nature of the instant formulations or for the specific virus infections to be treated.

Applicant again asserts that the mixtures of VLPs and vaccine antigens are clearly described.

Applicant's assertions have been considered. However, as discussed above, the nature of the "mixture" is not clear since the term encompasses fusions of two or more distinct entities into one mass and merely being in the same proximity. As stated in the previous Office action, it cannot be determined from the claim language whether the HBsAg is encapsulated within the various VLPs, or if the VLP and HBsAg are forming a chimeric molecule, or whether it is intended that the VLPs and HBsAg are co-administered as separate entities. Similarly, it cannot be determined how the vaccine antigens of claims 31-33 comprise the different nucleocapsid antigens. There is no teaching in the specification that would enable the skilled artisan a way to make HBsAg encapsulated within the various VLPs or making a chimeric molecule comprising the VLP and HBsAg or a vaccine antigen comprising a nucleocapsid antigen. The specification only teaches "mixing" two antigens together; see page 5, line 28, page 6, line 3, and page 7, line 19.

Applicant argues that adjuvants are effective against the immune response in general and that the ordinary artisan would have a reasonable expectation that the vaccine mixture would be effective with any vaccine antigen and reviews the data obtained from mice in the examples of

the disclosure. In addition, applicant asserts that the instant formulations are not limited to the longevity of the immune response elicited once administered. Applicant further asserts that the chimpanzee is not the only acceptable animal model for the study of HCV and that the Coursaget et al. reference cited by the Office provides evidence that various animal models are accepted by those skilled in the vaccine art. In response to the Farrell et al. reference, applicant states that the instant specification or claims make no assertions that the instant formulations overcome every problem in vaccine therapy, the claims are drawn to a composition with therapeutic efficacy. In conclusion, applicant asserts that the claimed invention would not pose undue experimentation for the skilled artisan with the immune response data generated by the instant mouse model.

Applicant's arguments have been considered, but are found to be unpersuasive. It is maintained that the instant vaccine formulations would not be considered effective as a therapeutic or a preventative against any antigen by the skilled artisan. The instant specification and working examples therein do not provide guidance or data with respect to either amelioration or prevention of any viral disease. The working examples are limited to administering various antigen combinations to mice and monitoring antibody response. The length of time in which the antibody response lasts would be an indication of effectiveness. The period of time for effectiveness of the instant formulations is questionable because there is no data provided for length of time antibody was produced in the mouse model in response to the compositions. There is also no data that would indicate to the skilled artisan that mice developed an immune response sufficient to treat or prevent HBV, HCV, HPV, or any other infection. Applicant's assertion that chimpanzees are not the only accepted animal model for the study of HCV is unfounded since applicant has not provided evidence to refute the teachings of Lanford et al. In

addition, Coursaget et al. does not provide evidence that various animal models are accepted in the art for the study of HBV or HCV or any other virus. The reference discusses the study of papillomavirus only and does not offer data concerning appropriate animal models for other viruses. Coursaget et al. discusses the lack of predictability in animal models in the study of papillomavirus infections by teaching that although some success has been observed in mouse models of papillomavirus infection, animal models more relevant to humans, have demonstrated only poor results. Therefore, it is concluded that even if there were data indicating effectiveness in treating or preventing papillomavirus infection with the instant composition in the mouse model, the skilled artisan would doubt its efficacy in other animal models or humans. Farrell et al. discusses challenges that still exist in developing HBV therapeutics for long-term efficacy. The instant disclosure and the working examples do not address any of the concerns in the HBV vaccine art discussed by Farrell et al. Also, contrary to applicant's assertion that the instant formulations are limited to therapeutic efficacy on page 18 of the response, applicant is directed to review the scope of claims 23, 24, and 25. The skilled artisan could not predict how a subject would respond to the vaccine composition, or whether the vaccine would have any efficacy for treating infection or preventing it.

Therefore, due to the ambiguity of the claims, the scope of the claims which encompass treating and preventing any infection with the vaccine composition, the lack of guidance provided by the inventor for making encapsulated HBsAg or chimeric molecules, the lack of ability the skilled artisan would have in making these products, the lack of guidance provided by the inventor with regard to CTL responses or how long the antibody response lasted, the lack of working examples with an appropriate animal model, the lack of data in the working examples

demonstrating preventative capabilities of the vaccine upon challenge and treatment capabilities of the vaccine when administered during infection, the lack of predictability in the vaccine art, and the undeveloped state of the art, it is maintained that an undue amount of experimentation would be required of the skilled artisan to make or use the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 11-14, 20, 21, and 28-30 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Balmelli et al. (Journal of Virology. Oct. 1998; 72 (10): 8220-8229).

Balmelli et al. teaches a vaccine formulation comprising

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11-14, 20, 21, 28-30 rejected under 35 U.S.C. 103(a) as being unpatentable over Lowy et al. (US 5,618,536) and Rose et al. (US 6,153,201).

The claims are drawn to a vaccine formulation suitable for nasal administration comprising a virus-like particle (VLP) and a vaccine antigen as well as a second antigen. The VLP and the vaccine antigen each enhance the immune response.

Lowy et al. teaches a papillomavirus VLP comprising L1 and L2. The vaccine formulation also comprises other antigens, such as E7 or E6 and the immune response to each antigen is enhanced upon administration. See claims 1-10, 14, 15, column 4, line 22 to column 5, line 50, , column 6, lines 31-58, , column 7, lines 27-65, column 14, line 49 to column 16, line 31. Lowy et al. does not teach nasal administration.

However, Rose et al. teaches a method of inducing an immune response against papillomavirus infection by orally administering papillomavirus VLPs. The formulations of Rose et al. are also administered intranasally. See claims 1-6 and column 9, lines 32-36.

One of ordinary skill in the art at the time the invention was made would have been motivated to administer the vaccine formulation of Lowy et al. by the intranasal route taught by Rose et al. for ease of administration and more cost effective to produce, see column 10, line 58 to column 11, line 17 of Rose et al. One of ordinary skill in the art at the time the invention was made would have been further motivated to administer the vaccine formulation of Lowy et al. by the method taught by Rose et al. to directly administer to a host the vaccine formulation to induce neutralizing antibodies against the papillomavirus antigens. These neutralizing antibodies generated by administration of papillomavirus VLPs induce protection against papillomavirus infection. See Figures 17-19 and column 8, line 61 to column 10, line 57 of Rose et al. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for producing the claimed invention because both references use papillomavirus-like

particles as vaccine formulations. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at time the invention was made, absent unexpected results.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SAF
Shanon Foley/SAF
May 31, 2002

James C. Housel 6/3/02
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